REMARKS

Claims 1, 5, 8-11, 19, 25 and 26 are in this application. Claims 2-3, 6, 7, 12-18 and 20-24 have been cancelled. Claims 1, 11, 19 and 25 have been amended as described below. Claim 26 is allowed.

The present invention is directed to a once-a-day controlled release pharmaceutical tablet composition for per oral administration consisting of a single unit fast release layer and a single unit extended release layer, which comprises 200mg micronized nimesulide having average particle size below 5 microns wherein said micronized nimesulide being present in the fast release layer and in the extended release layer and wherein said release controlling materials present in said extended release layer are biodegradable and a process for making a once-a-day controlled release pharmaceutical tablet composition for per oral administration consisting of a single unit fast release layer and a single unit extended release layer, which comprises 200mg micronized nimesulide having average particle size below 5 microns wherein said micronized nimesulide being present in the fast release layer and in the extended release layer and wherein said release controlling materials present in said extended release layer are biodegradable.

The invention defined by independent Claim 1 is a once-a-day controlled release pharmaceutical tablet composition for per oral administration consisting of a single unit fast release layer and a single unit extended release layer, which comprises 200mg micronized nimesulide having average particle size below 5 microns as an active drug from 20% to 70% w/w of the tablet composition, one or more release controlling materials in an amount from 8% to 20% w/w to control the release of said micronized nimesulide from said composition and

pharmaceutical excipients from 30% to 60% w/w of the tablet composition, wherein said micronized nimesulide being present in the fast release layer and in the extended release layer.

Applicants' again want to thank the Examiner and his supervisor for discussing this application with applicants' representative.

According to the Examiner claims 1, 5, 8-11, 19 and 25 are rejected under 35 USC 112, first paragraph as failing to comply with the written description requirement. This is respectfully traversed.

According to the Examiner the inclusion of cellulose acetate butyrate, cellulose acetate propionate, cellulose acetate trimellitate, polyalkylene polyols, and gums being biodegradable is new matter.

Support for this is found on page 6 of the application.

However to expedite prosecution and obtain allowance of this application, claims 1, 11, 19 and 25 have been amended to delete these terms.

Therefore, it is respectfully requested that this rejection be withdrawn.

The Examiner again states that claims 1, 5, 8-11, 19-25 are obvious over Skinhoj et al (US 6599529; 7/29/03), Saslawski et al. (WO 99/33448; 7/8/99) in view of Gibson et al. (US 6426340; 7/30/02) based on US Provisional 60/018202; 5/23/96). This is again respectfully traversed.

On page 5 in the penultimate line of the Office Action the Examiner states that the "claims state that the HPMC is biodegradable." Yet in the first full paragraph on page 9 of the Office Action, the Examiner "reiterates that there is no recitation in the instant claims that the release controlling material is biodegradable." The language " release controlling materials

present in said extended release layer are biodegradable" is included in claims 1, 11 and 25 and the language used in claim 19 is "biodegradable release controlling material". Clearly the claims include that the release controlling material is biodegradable.

The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 82 USPQ2d 1385, 1396 (2007) noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Federal Circuit has stated that "rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). See also *KSR*, at 1396. In this case, there is no rational basis to support the Examiner's assertion that applicants' invention would be obvious in view of Skinhoj et al (US 6599529; 7/29/03), Saslawski et al. (WO 99/33448; 7/8/99) in view of Gibson et al. (US 6426340; 7/30/02) based on US Provisional 60/018202.

The combination of Saslawski (WO '448) and Skinhoj ('529) do not teach, suggest or provide one of skill in the art with the motivation to prepare a composition as claimed in Claims 1, 5, 8-10, 19, and 25 or to develop the process of Claim 11.

Saslawski et al. teach away from Claim 1, as presented herein. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant" *In re Gurley* 27 F.3d 551, 553 (Fed. Cir. 1994); *see KSR*, 127 S. Ct. at 1739-40 (explaining that when the prior art teaches away from a combination, that combination is more likely to be non-obvious).

These references do not teach, suggest or provide one of skill in the art with the

motivation to prepare a composition wherein the release controlling materials in the extended release layer are biodegradable.

Further, these references do not teach, suggest or provide one of skill in the art with the motivation to prepare a once-a-day controlled release tablet composition for peroral administration consisting of a single unit fast release layer and a single unit extended release layer wherein micronized nimesulide having average particle size below 5 microns is present in the fast release layer and the extended release layer.

As argued previously, Saslawski et al. teach a multilayer tablet that can be made up of two layers i.e. a first outer layer (immediate or fast release layer) and second layer in contact with the first layer (prolonged release layer containing a **nonbiodegradable, inert porous polymeric matrix** in which the active substance is dispersed). See page 2, lines 19-30. Saslawski et al teach that the second layer constitutes an inert matrix that does not become eroded and does not swell in an aqueous medium (See page 3, line 33-35) and that the essential constituents of the second prolonged-release layer are polymeric materials which confer on it its inert and nonbiodegradable character. The polymers or copolymers are insoluble in water, not forming a gel and are discharged intact by the body (See page 12, lines 10-15).

Saslawski discloses specifically **the use of nonbiodegradable** inert material in the second layer and not **biodegradable material** as claimed in independent claims 1, 11, 19 and 25 of the present invention. **The release controlling materials as included in the claims do not include non-biodegradable, inert, polymeric matrix as described in Saslawski et al.**

As stated above, the key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 82 USPQ2d 1385, 1396 (2007) noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made

explicit. The Federal Circuit has stated that "rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). See also *KSR*, 550 U.S. 82 USPQ2d at 1396.

The Examiner states on page 6 of the Official Action of December 18, 2009 that HPMC used in Saslawski et al as well as in the instant invention is in overlapping concentration ranges, therefore irrespective of what HPMC may be called it should render the same effect or benefit. The Examiner further argues that Saslawski et al teach 0.5 to 25% wt binder such as HPMC (page 11, lines 25-28, page12, lines 3-7) therefore HPMC in Saslawski et al., and the instant invention would be expected to yield the same effect or benefit since the invention teach overlapping concentration ranges for HPMC.

The applicants again draw the Examiner's attention to the fact that in spite of using overlapping concentration of HPMC at the lower of the range by applicants, the subject matter of invention as claimed herein is clearly distinct from Saslawski et al. The applicants again refer to the evidence filed previously to show that HPMC used by Saslawski et al., would not result into same benefit or effect as obtained by present invention. In addition, as explained before and again in this paper, the claims provide that the release controlling material is biodegradable. This clearly distinguishes the claimed invention from the art cited by the Examiner.

Saslawski et al., has not disclosed different grades or viscosity of HPMC and its use other than binder or disintegrator which is a different function from that claimed in the claims at issue in this appeal. Saslawski et al., describe release of 9 hours (Once-daily dosing) due to the presence of **non-biodegradable polymer**, not by the presence of binder e.g. HPMC. In all examples of Saslawski et al., HPMC has been used in an amount which acts as a binder, not

for sustaining the release of drug for 9 hours to provide once-daily dosing. One skilled in the art would never use HPMC taught by Saslawski et al., for sustaining the release of drug. An ordinary person skilled in the art would never confuse between HPMC as a binder and HPMC as a release controlling material which is well understood to be used based upon its viscosity and molecular weight grades. As known by a person skilled in the art, when HPMC is used as a binder it is used in a particular grade and viscosity which will only function as a binder and not function as a release controlling agent even used in any amount. This is shown in Sarfraz et al. which is of record in this application file.

HPMC as a release controlling material has not been used by Saslawski et al. Saslawski's invention describes making a composition of NSAID by utilizing non-biodegradable polymer as rate controlling material while applicant's composition uses non-biodegradable polymer.

Evidence is already of record that describe that these release controlling materials according to the present invention are biodegradable and/or gel or swell and erode in the presence of water. As described above, these release controlling materials differ from those disclosed in Saslawski et al.

Therefore, an HPMC-based formulation prepared according to Saslawski et al., (even used up to 25%) will not provide the same benefit or effect and requires that the formulation contains **non-biodegradable polymer**. Saslawski et al clearly and specifically teaches away from using hydrophilic/biodegradable polymer for sustaining the release of drug and doing what applicants' have done.

The composition prepared according to the present invention does not contain any non-biodegradable polymer but it contains hydrophilic polymers which are biodegradable in

nature and/or swellable in water thus, provides once-daily administration of nimesulide.

One of ordinary skill in the art following the teachings of Saslawski et al. would be taught to formulate a composition having first outer layer allowing immediate release of a first active substance (page 2, line 3-26) and a second layer containing a **nonbiodegradable, inert porous polymeric matrix** (page 2, lines 27-30) and that these polymers or copolymers [are] insoluble in water (but not forming a gel either upon immersion in an aqueous medium) (page 3, lines 33-35). One of ordinary skill in the art would find no motivation to provide a formulation as defined in independent Claims 1 and 25 and the process of Claim 11 of nimesulide with single unit fast release layer comprising micronized nimesulide having average particle size below 5 microns and single unit extended release layer comprising micronized nimesulide having average particle size below 5 microns and **biodegradable release controlling materials** selected from a group consisting of methyl cellulose, ethyl cellulose, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, cellulose acetate phthalate, cellulose acetate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, carbomers, polycarbophils, and gelatins in an amount effective to control the release of nimesulide from the extended release layer.

Saslawski et al neither teach nor suggest the use of biodegradable material in second layer (extended release layer) for prolonging the action of NSAIDs, more preferably nimesulide.

The Examiner still maintains that it is acceptable to equate the drug nimesulide with the drug naproxen. There is no basis for the Examiner's statement that according to Skinhoj et al. ('529) naproxen and nimesulide are equivalent. In column 16, line 58- column 17, line 27 of Skinhoj ('529) while there is a list of different types of NSAIDs, naproxen is listed as an

arylpropionic acid derivative and nimesulide is included in the category of others (column 17, line 23), not as an arylpropionic derivative. Nimesulide and naproxen are two different compounds and have totally different structures.

The Examiner also attempts to rely on the disclosure of nimesulide from the list of NSAID's in Skinhoj et al. ('529) for stating that it would be obvious to substitute nimesulide for naproxen. One skilled in the art has no reasonable expectation of success that all compounds that are classified under a broad category such as "NSAIDs" can all be formulated in the same way. While the applicants' have provided evidence explaining the differences between nimesulide and naproxen, the Examiner has not provided any references or basis to support his statement. One of ordinary skill in the art would not consider that all of the NSAIDs listed in column 16, line 58-column 17, line 27 are equivalent or that anyone could be substituted for another. For example one of ordinary skill in the art knows that acetylsalicylic acid is not equivalent to ibuprofen or acematicin so there is no basis for stating that just because two compounds are grouped together under a broad heading of NSAIDs that naproxen and nimesulide are equivalent, that one could be substituted for the other or that they can both be formulated in the same way.

It is emphasized that **neither nimesulide nor any other sulfonanilide derivative has been disclosed by Saslawski et al.** and Skinhoj does not describe nor suggest the use of nimesulide in both the immediate release layer and extended release layer plus the claimed release controlling material(s) in the extended release layer. There is no way to combine these references to teach a composition comprising nimesulide in the fast release layer and in the extended release layer wherein said release controlling materials present in said extended release layer are biodegradable. **Neither reference teaches biodegradable release controlling materials in an extended release layer and as discussed above neither reference teaches that nimesulide can be substituted for naproxen.**

Although Skinhoj et al., describes certain types of NSAIDs, that include nimesulide and naproxen but it does not teach or suggest micronized nimesulide having average particle size below 5 microns. Applicant herein argues that no prior art (either Skinhoj et al. or Saslawski et al.) mention the use of micronized nimesulide having average particle size below 5 microns. (*See Merck & Co., Inc.,* v. *Biocraft Laboratories*, 874 F.2d 804) (CAFC). The claims include (i) 200 mg micronized nimesulide having average particle size below 5 microns and; (ii) release controlling materials of the extended release layer which are biodegradable. **The release controlling materials are NOT nonbiodegradable, inert porous polymeric matrix like the copolymers of (meth)acrylic acid derivatives as required by Saslawski et al.**

There is no way for one skill in the art to invent the claimed invention given the disclosures of Saslawski and Skinhoj. Saslawski teaches a second layer consisting of **nonbiodegradable, inert porous polymeric matrix** and does not disclose the use of nimesulide. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant" *In re Gurley* 27 F.3d 551, 553 (Fed. Cir. 1994); *see KSR*, 127 S. Ct. at 1739-40 (explaining that when the prior art teaches away from a combination, that combination is more likely to be nonobvious). Saslawski et al. does not teach or suggest biodegradable release controlling materials present in said extended release layer and can be considered to teach away from this.

"All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). When evaluating claims for obviousness under **35 U.S.C. 103**, all the limitations of the claims must be considered and given weight, including limitations which do not find support in the specification as originally filed (i.e., new matter). *Ex parte Grasselli*, 231 USPQ 393 (Bd. App.

1983) *aff'd mem.* 738 F.2d 453 (Fed. Cir. 1984) (Claim to a catalyst expressly excluded the presence of sulfur, halogen, uranium, and a combination of vanadium and phosphorous. Although the negative limitations excluding these elements did not appear in the specification as filed, it was error to disregard these limitations when determining whether the claimed invention would have been obvious in view of the prior art.) (See MPEP 2143.03)

The independent Claims 1, 11 and 25 define a once-a-day controlled release pharmaceutical tablet composition for peroral administration consisting of a single unit fast release layer and a single unit extended release layer, which comprises 200 mg micronized nimesulide having average particle size below 5 microns as an active drug from 20% to 70% w/w of the tablet composition, one or more release controlling materials in an amount from 8% to 20 % w/w to control the release of said micronized nimesulide from said composition and pharmaceutical excipients from 30% to 60% w/w of the tablet composition, wherein said micronized nimesulide being present in the fast release layer and in the extended release layer and wherein said release controlling materials present in said extended release layer are biodegradable. The release controlling materials used in the claimed invention are NOT NONBIODEGRADABLE, inert, porous polymeric matrix like the copolymers of (meth)acrylic acid derivatives as required by Saslawski et al. It is clear that the claims are patentable and not obvious over the cited references.

The claims are clearly patentable over Skinhoj et al ., and Saslawski et al., and as such are clearly patentable over these references in combination with Gibson et al. which teaches the use of silicon dioxide.

Neither Skinhoj nor Saslawski et al., nor Gibson et al., singly or in combination, teach or suggest a once-a-day controlled release composition of nimesulide consisting of single unit fast release layer comprising micronized nimesulide having average particle below 5

microns and single unit extended release layer comprising micronized nimesulide having average particle below 5 microns and one or more biodegradable release controlling materials, wherein the release controlling materials present in the extended release layer are specified from a group consisting of methyl cellulose, ethyl cellulose, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, cellulose acetate phthalate, cellulose acetate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, carbomers, polycarbophils and gelatins.

In light of the scope and content of the prior art and in light of the differences between the prior art and the claims, applicant respectfully submits that Claims 1, 5, 8-11, 19 and 25 are patentable over the combined teachings of Skinhoj et al., Saslawski et al., and Gibson et al.

It is respectfully requested that this rejection be withdrawn.

In light of the amendments to the claims and the arguments presented herein, this application is clearly in condition for allowance.

Respectfully submitted,

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